REMARKS

The Office Action dated August 24, 2004 presents the examination of claims 28, 29, and 36. Claims 26, 27, 30-35, and 37-53 are withdrawn from consideration. Claims 26 and 28 are amended to reflect the elected invention. Claim 29 is canceled. No new matter is added to the application.

Election/Restriction

On page 1 of the Office Action (i.e., the Office Action Summary), the Examiner indicates that claim 26 is withdrawn from consideration. However, it appears the Examiner has rejoined claim 26 for consideration since it stands rejected under 35 U.S.C. §§ 101 and 112, first paragraph. The Examiner is respectfully requested to clarify the status of claim 26.

Information Disclosure Statement

The Examiner states that all of the references cited on the PTO-1449 forms of January 22, 2002 and June 12, 2002 have been considered, but that only one of the forms has been initialed and returned. Applicants did not receive a copy of the initialed form. The Examiner is respectfully requested to provide Applicants with a copy of the initialed PTO-1449 form.

Claim Objections

The Examiner objects to claims 28, 29, and 36 for minor informalities. Claim 29 is canceled, thus rendering the objection thereto moot. Applicants respectfully traverse the objection to pending claims 28 and 36. Reconsideration and withdrawal of the instant objection are respectfully requested.

In order to overcome the claim objections, claim 28 is amended into independent form. Withdrawal of the instant objection is therefore respectfully requested.

Rejection under 35 U.S.C. § 101

The Examiner rejects claims 26, 28, 29, and 36 under 35 U.S.C. § 101 for an alleged lack of utility. Claim 29 is canceled, thus rendering the rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration and withdrawal of the instant rejection are respectfully requested.

Applicants respectfully submit that the Examiner has issued an improper utility rejection. The Examiner is reminded that the initial burden is on the USPTO to establish a *prima facie* case of lack of utility. In this regard, "[t]o properly reject a claimed invention under 35 U.S.C. § 101, the Office must (A) make a *prima facie* showing that the claimed invention lacks utility, and (B)

provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing." U.S. Pat. & Trademark Off., *Manual Pat. Examining Proc.* § 2107.02 (8th ed. Rev. 2 2004). See also, In re Gaubert, 524 F.2d 1222 (CCPA 1975).

In the instant case, the Examiner has failed to make a *prima facie* case of lack of utility. The present invention is directed to novel, naturally occurring splice variants of the CD40 receptor (CD40R). On page 4 of the Office Action, the Examiner acknowledges that the instant specification asserts that the disclosed CD40 splice variants retain ligand binding capabilities, and thusly have a well-established utility. However, the Examiner asserts that the claimed utility is not credible because the instant specification allegedly fails to *demonstrate* that the CD40 receptor actually binds to CD40 ligands.

The Examiner's attempt to shift the burden to Applicants to show actual ligand binding of the splice variants of the CD40 receptor is clearly improper. The Examiner is reminded that the burden is not on Applicants to demonstrate actual biological activity. Instead, the burden is on the Examiner to show by a preponderance of the evidence that the asserted utility is not credible:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds

> in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 503 F.2d, 1380, 1391 (CCPA 1974) (emphasis in original).

The Examiner has provided no scientifically reasonable grounds for alleging that the skilled artisan would not believe that the inventive CD40 splice variants retain ligand binding capabilities. In this regard, the Examiner does not point to any evidentiary or documentary evidence (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) which suggests or discloses that alternative splice variants of CD40 lose their ability to bind ligand. Instead, the Examiner merely states, "The CD40 receptor claimed in the instant application shares only 135 amino acid residues with the native human CD40 receptor, and contains 25 amino acid residues that are not shared by the human CD40 receptor." However, as even acknowledged by the Examiner, the inventive CD40 splice variants retain the extracellular domain of the wild-type CD40. Thus, contrary to the Examiner's remarks, the skilled artisan would not automatically assume that the inventive CD40 splice variants have lost their ability to bind CD40 ligand.

Based upon the above, the Examiner's allegations do not rise to the standard sufficient to rebut the statement of utility provided in the specification. For this reason, the rejection is improper and must be withdrawn.

Even though the Examiner has failed to make a *prima facie* case of lack of utility, in the interest of compact prosecution, Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 executed by Amir Toporik which shows the biological role of the inventive protein.

Claim 28, as amended, recites the elected amino acid sequence of SEQ ID NO: 7. The Declaration describes experiments performed with the CD40 alternative splice variants of the present invention, and in particular the variant comprising the amino acid sequence of SEQ ID NO: 7. These experiments show that the variants are agonists and clearly are capable of binding to CD40 ligand, as particularly shown in the FACS experimental results.

Furthermore, the CD40 splice variant encoded by SEQ ID NO: 7 exhibits strong agonist behavior, as particularly shown from the results of the RANTES experiment. As known in the art, RANTES (also known as CCL5) is a cytokine belonging to the interleukin-8 superfamily. The secretion of RANTES is indicative of T cell activation, and therefore can be used as

a measure for determining whether a particular therapy may block or, alternatively, increase T cell activation. As a measure of T cell activation, increased RANTES production is directly indicative of a direct therapeutic effect of the CD40 splice variants of the present invention.

Further, RANTES has a number of effects which are important for controlling or preventing disease, for example by activating natural killer cells known as CHAK cells. CHAK cells have been suggested as a therapy for cancer patients, since they attack cancer cells. RANTES is also an important factor for suppressing HIV infection and also for decreasing progression thereof. See, Maghazachi et al., *The FASEB Journal*, 1998, 12:913-919, a copy of which is attached hereto.

As shown in the experimental data described in the attached Declaration, the CD40 splice variants of the present invention resulted in an increase in RANTES secretion, and therefore are strong agonists. This finding shows that the splice variants of human CD40 disclosed in the instant specification retain their ability to bind ligand, and thusly have a well-established utility.

Non-limiting examples of diseases for which an agonist such as the CD40 splice variant encoded by SEQ ID NO: 7 could be useful include: hematological malignancies, cancers, epithelial neoplasia,

nasopharyngeal carcinoma, osteosarcoma, neuroblastoma and bladder carcinoma, AIDS-related lymphoma, and impaired renal function, including chronic renal failure, haemodialysis, and chronic ambulatory peritoneal dialysis (CAPD) patients.

In summary, an amino acid sequence encoded by SEQ ID NO: 7 possesses a determined function and biological significance, contrary to the Examiner's remarks. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

Enablement

The Examiner rejects claims 26, 28, 29, and 36 under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. Claim 29 is canceled, thus rendering the rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that since the claimed invention allegedly possesses no utility, one skilled in the art would not know how to make and use the invention. However, as noted above, the claimed invention fully complies with the utility requirement of 35 U.S.C. § 101. As such, the skilled artisan could readily make and use the invention without undue experimentation.

Withdrawal of the instant rejection is therefore respectfully requested.

Written Description

The Examiner also rejects claims 26, 28, 29, and 36 under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description in the specification. Claim 29 is canceled, thus rendering the rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that the specification does not provide the structure of "all" possible amino acid modifications (i.e., additions, substitutions, deletions, etc.) to the polypeptide of SEQ ID NO: 7. Claim 28, as amended, is directed to an isolated amino acid sequence comprising SEQ ID NO: 7. Applicants respectfully submit that an amino acid sequence comprising SEQ ID NO: 7 is fully described and supported by the instant specification. In this regard, the specification discloses SEQ ID NO: 7 and its relationship with wild-type CD40. In addition, CD40 is a well-studied protein, such that the domain structure of the protein is well known in the art. The instant specification clearly describes these different domains and their relationship to

the function of the protein. See, for example, Figures 1, 4, 5, and 6.

For these reasons, the pending claims fully comply with 35 U.S.C. § 112, first paragraph. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 28, 29, and 36 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Claim 29 is canceled, thus rendering the rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that the recitation of "in which one or more amino acids have been added, deleted, replaced or chemically modified..." is indefinite. In order to overcome the rejection, but not to acquiesce to the Examiner's position, section (ii) of claim 28 is deleted.

Applicants respectfully submit that the pending claims particularly point out and distinctly claim the subject matter of the present invention. As such, all claims fully comply with 35 U.S.C. § 112, second paragraph. Withdrawal of the instant rejection is therefore respectfully requested.

Rejections under 35 U.S.C. § 102

Stamenkovic et al.

The Examiner rejects claim 28 under 35 U.S.C. § 102(b) for allegedly being anticipated by Stamenkovic et al. (Accession No. A60771). Applicants respectfully traverse. Reconsideration and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts that the sequence of Accession No. A60771 shares 86% homology to SEQ ID NO: 7 of the present invention. Claim 28, as amended, is directed to an isolated amino acid sequence comprising SEQ ID NO: 7. Accession No. A60771 is not an amino acid sequence comprising SEQ ID NO: 7.

Thus, Stamenkovic et al. fails to anticipate the present invention as recited in the pending claims. Withdrawal of the instant rejection is therefore respectfully requested.

Aruffo '459

The Examiner rejects claims 28 and 36 under 35 U.S.C. § 102(b) for allegedly being anticipated by Aruffo '459 (U.S. Patent 6,376,459). Applicants respectfully traverse. Reconsideration and withdrawal of the instant rejection are respectfully requested.

Aruffo '459 discloses the extracellular domain of wild-type CD40 as part of a fusion protein, which is capable of specifically binding to the CD40 ligand (termed a "counter-receptor" in the

reference). Claim 28, as amended, is directed to an isolated amino acid sequence comprising SEQ ID NO: 7. Aruffo '459 fails to disclose or suggest the subject matter of claim 28.

SEQ ID NO: 7 is a splice variant of CD40. Specifically, SEQ ID NO: 7 lacks one of the extracellular exons (i.e., exon 5) due to the mechanism of exon exclusion. This splice variant furthermore possesses a unique sequence that is absent from the wild-type CD40 receptor. In particular, SEQ ID NO: 7 possesses amino acids 136-160, which are absent from the CD40 taught by Aruffo '459. As a consequence, it is not sufficient to consider only the identity portions of sequences reported by a local sequence alignment program in order to appreciate the distinctive features of the splice variants disclosed in the present application. Only by comparing the entire sequences of the present invention with the entire sequences of the prior art, for example by a global alignment, would the amount of relatedness as well as the relevant differences of the sequences be adequately assessed.

For these reasons, Aruffo '459 fails to anticipate the present invention as recited in the pending claims. Withdrawal of the instant rejection is therefore respectfully requested.

Conclusion

Applicants respectfully submit that the above remarks and/or amendments fully address and overcome the outstanding rejections and objections. For the foregoing reasons, Applicants respectfully request the Examiner to withdraw all of the outstanding rejections and objections, and to issue a Notice of Allowance indicating the patentability of the present claims. Early and favorable action of the merits of the present application is thereby respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Maghazachi et al., *The FASEB Journal*, 1998, 12:913-919
Declaration Under 37 C.F.R. 1.132